REMARKS

Claims 1-11, 14, 43-63, 67, and 68 are pending in the application. Claims 14, 44-59, and 67 are allowed and claims 1-11, 43, 61-63, and 68 are rejected. Claims 1, 6, 7, 44, 49, 50, and 52 are amended. As an initial matter, Applicants wish to thank Examiner O'Hara for speaking with them about the application. In view of this discussion, Applicants have amended the pending claims to clarify that the mutant G protein-coupled receptor comprises a mutation in an amino acid of the receptor. Support for the amendment is found in the specification and claims as originally filed. No new matter has been added.

In view of the present amendment and remarks Applicants believe that the claims are in condition for allowance. Should the Office disagree, Applicants respectfully request that the Office contact Applicants' undersigned representative by telephone so that an interview may be scheduled prior to the mailing of any final Office action.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-11, 43, 61-63, and 68, which are directed to mutant mammalian G protein-coupled receptors, are rejected under 35 U.S.C. § 112, first paragraph, as lacking an adequate written description. Applicants believe that this rejection was made in error because it does not set forth new grounds for rejection, but merely repeats rejections that were previously made in the Office action mailed April 29, 2004 (see, page 3, line 7, to page 5, line 7, and page 7, line 16, to page 9, line 19). These rejections were overcome in the reply filed on October 29, 2004, as evidenced in the Ex Parte Quayle Action that was mailed on May 13, 2005, which stated that the application was in condition for allowance. Nevertheless, for completeness sake, Applicants respectfully submit the following remarks showing that there is sufficient written description in Applicants' specification regarding the claimed molecules, to inform a skilled artisan that Applicants were in possession of the claimed invention at the time the application was filed, as required by section 112, first paragraph (see M.P.E.P. §2163.02).

During a telephone conference with Applicants on December 19, 2005, the Examiner expressed concern that the phrase "seventh transmembrane domain" was not adequately described. Applicants note that G protein-coupled receptors are often referred to as seven

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transmembrane domain receptors, and that one skilled in the art would readily appreciate the position of the seventh transmembrane domain within the receptor.

For reasons discussed in detail below, the instant specification satisfies this requirement for the claimed invention. It is Applicants' position that the claimed genus of the mutant GPCRs of the present invention is defined by structural features that are described in the specification, recited in the claims, and commonly possessed by its members. In particular, the structure of the claimed genus is taught in the specification, i.e., the structure of the mutant GPCR, the corresponding the amino acid motif [X1X2X3X4] and the position of the mutation within the amino acid motifs (see page 7, line 17 through page 8, line 40 of the specification). Furthermore, this structure was already well-know in the art through such publications as, for example, Navarro et al. WO/92/18641.

In addition, the structural features, active domains, binding regions and other features that are common to GPCRs in general and the chemokine receptors of subfamily A were well known to those of ordinary skill in the art at the time the application was filed. Indeed, this is acknowledged in the Gether reference. Furthermore, a specific subset of chemokine receptors, i.e., the chemokine α family receptors, is fully described in the instant specification at page 2, lines 18-31, Table 1 and page 3, lines 5-6.

Contrary to the Examiner's assertion, Applicants respectfully submit that the instant specification teaches distinguishing structural features within the claimed genus. For example, the instant specification discloses the amino acid sequence of the rabbit IL8A receptor showing putative membrane spanning domains, e.g., Arg73 (1st intracellular loop), Met246 (3rd intracellular loop) and Gly320 (C-terminal tail) (see page 10, lines 19-21 of the specification. Moreover, G protein-coupled receptors of the subfamily A are known molecules with a conserved structure as taught by Gether.

In summary, Applicants have described a genus of mutant GPCRs based on structural features that are common to a substantial portion of the genus and have provided within the instant specification the amino acid motifs and the mutations within the amino acid motif that possess these features. Accordingly, Applicants submit that the present invention satisfies the requirements of 35 U.S.C. §112, first paragraph.

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Rejections under 35 U.S.C. § 102

Claims 1, 5, 8, 11, and 43, which are directed to mutant mammalian G protein-coupled receptors, are rejected under 35 U.S.C. § 102 as anticipated by Kluxen et al., *Proc. Nat'l Acad. Sci.*, 89: 4618-4622, 1992 (hereinafter, "Kluxen"). Kluxen describes the cloning of a cDNA encoding a somatostatin receptor, referred to as somatotropin release-inhibiting factor (SRIF) receptor, from rat cortex and hippocampus. In support of the rejection, the Office asserts that the Kluxen reference anticipates the claimed invention because i) the SRIF receptor amino acid sequence anticipates the structure of the claimed mutant G protein-coupled receptors; ii) the SRIF receptor anticipates the function of the claimed mutant G protein-coupled receptor; and iii) the claims are also anticipated by a wild-type IL8 receptor. For the reasons discussed below, Applicants disagree with the present rejection and request that it be withdrawn.

I. Standard for Anticipation.

For a reference to serve as the basis for an anticipation rejection that reference must disclose each and every element of present in the claim. M.P.E.P. 2131 "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 2001). Kluxen fails to disclose each and every element of Applicants' claimed invention and, therefore, cannot destroy the novelty of Applicants' claimed invention.

II. Kluxen's wild-type G protein-coupled receptor fails to anticipate the structure of the claimed mutant receptor.

Applicants' claims are directed to mutant mammalian G protein-coupled receptors having amino acid sequences that differ from the sequence of wild-type chemokine α G protein-coupled receptors. In contrast, Kluxen describes the cloning and characterization of a wild-type rat brain somatostatin receptor (Abstract, page 4618, left column). This wild-type sequence was isolated by expression cloning from the developing hippocampi and cortexes of 6-day old rats (page 4622, left column, paragraph 1). Contrary to the Office's assertion, a wild-type sequence of SRIF cannot anticipate Applicants' claimed mutant protein sequence because a mutant sequence is by virtue of the mutations that it contains different from a wild-type sequence. The

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differences between mutant and wild-type proteins are described by Lodish et al., (Molecular Cell Biology. 4th ed. New York: W. H. Freeman & Co.; c2000; hereinafter "Lodish"); (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Search&db=books&doptcmdl=GenBookHL&term=wild-type+AND+mcb%5Bbook%5D+AND+105703%5Buid%5D&rid=mcb.chapter.1850), which is attached as Exhibit A.

> In practice, removing a protein is done indirectly by identifying organisms in which the nucleotide sequence of the gene encoding the protein is altered or deleted. Such **changes in the DNA sequence, called mutations**, can lead to loss of the encoded protein or to a change in its structure. The affected organisms, called mutants, are identified by virtue of differences in their appearance, physiology, behavior, or growth properties compared with normal, wild-type (nonmutant) organisms. **By comparing specific DNA sequences from mutant and normal organisms, researchers can correlate the abnormal features of the mutant organism with differences in the expression or structure of specific proteins**.

As Lodish makes clear, mutations are changes in a DNA sequence. Such changes are identified by comparing a mutant sequence to a wild-type reference sequence.

III. Kluxen's wild-type G protein-coupled receptor fails to anticipate the function of the claimed mutant receptor.

Applicants' claims require that the mutant receptor have particular functional characteristics; specifically, the mutant receptor generates a greater signal in response to ligand than the wild-type G protein-coupled receptor. The Office asserts that the SRIF receptor anticipates Applicants' claimed invention because the Office predicts that the SRIF receptor's response to somatostatin will be greater than the response of a galanin receptor to somatostatin. The Office states:

> The somatostatin receptor meets the functional limitation because it will have a larger response to somatostatin than will the galanin receptor. Thus, the somatostatin receptor, when compared to the galanin receptor, meets the structural and functional limitations in the claim. (Office action mailed September 19, 2005, page 7, second paragraph.)

As an initial matter, Applicants note that this is mere speculation on the part of the Office, and such speculation cannot serve as the basis for an anticipation rejection because to serve as an anticipation the reference must disclose each and every aspect of the claimed invention.

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M.P.E.P. 2163.01. Applicants' claims require that a mutant G protein-coupled receptor generate a greater signal in response to ligand than the wild-type G protein-coupled receptor. Kluxen fails to disclose any mutant G protein-coupled receptor, much less a mutant receptor having the signaling characteristics recited in Applicants' claims. Thus, this basis for the anticipation rejection should also be withdrawn.

IV. Applicants' describe exemplary mutant receptors having the recited structural and functional characteristics

Applicants' specification describes characteristic features that distinguish the claimed mutant receptors from wild-type receptors. For example, at pages 64-67, under the heading "Example 2. Creation of IL-8A Receptor Mutants," Applicants describe the introduction of alterations into the amino acid sequence of an exemplary wild-type receptor, the IL-8A receptor. At page 65, lines 23-30, Applicants teach that the sequence of mutant receptors differs from that of a wild-type receptor. Specifically, Applicants describe exemplary mutant IL-8A receptors having an arginine to tryptophan mutation at position 73; having a methionine to isoleucine mutation at amino acid position 246; and having a glycine to arginine mutation at amino acid position 320. Applicants also characterized the response of these mutant receptors to their ligand, IL8, and found that the mutant receptors had a significantly greater response to ligand than the wild-type receptor (page 66, lines 18-20). Such mutant IL-8A receptors exemplify the mutant receptors that fall within the scope of Applicants' claims.

In contrast, Kluxen fails to disclose <u>any</u> mutant receptor, much less a mutant G protein-coupled receptor that generates a greater signal in response to ligand than a wild-type receptor as required by the claims. Thus, the rejection of the claims for anticipation by Kluxen should be withdrawn.

V. A wild-type IL8 receptor cannot anticipate a mutant G protein-coupled receptor

The final basis for the anticipation rejection is that the claims are anticipated by a wild-type IL8 receptor. The Office states, "Further, since there is no upper limit to the mutations ("at least one") in the claims are anticipated in which the wild type GPCR [G protein-coupled

receptor] is the IL8 receptor. [*sic*]" Contrary to the Office's assertion, Applicants' claims require the presence of "at least one point mutation at a position in said amino acid motif." The motif includes four amino acids and therefore could include no more than four mutations within it. Thus, there is clearly an upper limit to the number of mutations that could be present in the motif. Moreover, as discussed above, a wild-type receptor, such as the IL8 receptor, cannot anticipate a mutant receptor because the mutant receptor has an amino acid sequence that differs from that of a wild-type receptor. Thus, a wild-type IL8 receptor cannot anticipate Applicants' claimed mutant G protein-coupled receptor, and this basis for the anticipation rejection should also be withdrawn.

As noted by the Office, mutations may be introduced during evolution or by directed mutagenesis in a laboratory. Applicants' claims are not limited to G protein-coupled receptors having only experimentally introduced mutations, but encompass any mutant receptor having the structural and functional limitations recited in the claims.

Rejections under 35 U.S.C. § 103

Claims 1-6, 8, 10-11, and 43, which are directed to mutant G protein-coupled receptors are further rejected as obvious over Kluxen in view of Hitzeman et al., U.S. Patent 5,618,676 (hereafter "Hitzeman"). The Office asserts that the SRIF receptor disclosed by Kluxen meets the structural and functional limitations of Applicants' claimed receptor, and that Hitzeman discloses the production of such receptors in yeast. Applicants respectfully disagree with the present rejection for the reasons detailed below and request that it be withdrawn.

I. Standard for obviousness

The test of obviousness requires that one compare the claimed "subject matter as a whole" with the prior art "to which said subject matter pertains" 35 U.S.C. § 103(a). To establish a *prima facie* case of obviousness, three criteria must be met. First, the prior art reference must teach or suggest all the claim limitations. Second, a suggestion or motivation to modify the reference or combine reference teachings must be present in the references or in the general knowledge present in the art. Third, there must be a reasonable expectation of success. M.P.E.P. 2143.

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II. Kluxen fails to teach or suggest Applicants' claimed invention

As discussed above, Kluxen describes the cloning and characterization of a wild-type somatostatin receptor, the SRIF receptor, that is expressed in regions of the developing brain. Kluxen fails to describe the sequence of any mutant receptor, nor can the sequence of a wild-type SRIF fall within the scope of Applicants' claims because the sequence of a mutant receptor is by definition different from the sequence of the wild-type receptor. In addition, Applicants' claims require that the mutant receptor generate a greater signal in response to ligand than the wild-type receptor. Kluxen fails to describe any mutant receptor, much less a mutant receptor having the required signaling characteristics. Thus, Kluxen fails to teach or suggest the structural and functional limitations recited in Applicants' claims.

In addition, Kluxen fails to teach or suggest modifying the wild-type SRIF receptor to obtain a mutant G protein-coupled receptor that would fall within the scope of Applicants' claimed invention. Kluxen merely describes the isolation and characterization of SRIF. Kluxen states:

> Based on these results we conclude that we have indeed cloned the cDNA that encodes the most commonly studied SRIF receptor type. The receptor is a member of the family of G-protein-coupled receptors with seven transmembrane regions. **The pharmacological profile of this receptor when expressed in the heterologous COS-1 cell system is indistinguishable from native SRIF receptors**, and the tissue distribution closely resembles that of the described SRIF binding sites. (page 4622, right column, third paragraph; emphasis added.)

Kluxen fails to teach or suggest introducing any mutation into the SRIF receptor, much less a mutation that would cause it to generate a greater signal in response to ligand than a wild-type receptor. In the absence of such a teaching, one skilled in the art would entirely lack the requisite motivation or expectation of success to modify the wild-type SRIF receptor described by Kluxen to obtain Applicants' claimed mutant receptor.

III. Hitzeman fails to teach or suggest Applicants' claimed invention

Hitzeman fails to remedy the deficiencies of Kluxen. Hitzeman merely describes protein production in yeast. Like Kluxen, Hitzeman fails to teach or suggest a mutant G protein-coupled receptor having the structure and function of Applicants' claimed mutant receptor. Moreover, Hitzeman fails to teach or suggest the introduction of any mutation into a G protein-coupled

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receptor, much less the introduction of a mutation that would produce a mutant receptor having the signaling characteristics of Applicants' claimed mutant receptor.

In sum, none of the cited references, alone or in combination, teaches or suggests a mutant G protein-coupled receptor having the specific structure and function recited in Applicants' claims. Thus, even if there were a motivation to combine the references, the combination would not put one of ordinary skill in the art in possession of all the elements of Applicants' claims. Moreover, none of the cited references teaches or suggests modifying the wild-type SRIF receptor described by Kluxen to obtain Applicants' claimed mutant receptor. In the absence of such a teaching, one skilled in the art would lack the requisite motivation or expectation of success to produce Applicants' claimed mutant G protein-coupled receptor and achieve a signal upon ligand interaction and activation that is greater than the signal generated by ligand interaction and activation of the wild-type receptor. Accordingly, the obviousness rejection should also be withdrawn.

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CONCLUSION

In view of the above remarks, Applicants believe the pending application is in condition for allowance. Accordingly, the Office is respectfully requested to pass this application to issue. Should any of the claims not be found to be allowable, Applicants respectfully request the Office to telephone Applicants' undersigned representative at the number below so that a telephonic interview may be scheduled. Applicants thank the Office in advance for this courtesy.

Dated: December 19, 2005

Respectfully submitted,

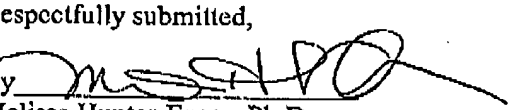
By 

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Exhibit A

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Molecular Cell Biology

8. Genetic Analysis in Cell Biology

In previous chapters, we learned how proteins — the cell's working molecules — are isolated, how their structures are determined, and how the genes encoding known proteins are cloned. Our primary concern, however, is what a protein does in the organism. In principle, the in vivo function of a protein can be deduced by seeing what effect removal of the protein has on the cell or, in the case of a multicellular organism, on the whole organism. In practice, removing a protein is done indirectly by identifying organisms in which the nucleotide sequence of the gene encoding the protein is altered or deleted. Such changes in the DNA sequence, called mutations, can lead to loss of the encoded protein or to a change in its structure. The affected organisms, called *mutants*, are identified by virtue of differences in their appearance, physiology, behavior, or growth properties compared with normal, **wild-type** (nonmutant) organisms. By comparing specific DNA sequences from mutant and normal organisms, researchers can correlate the abnormal features of the mutant organism with differences in the expression or structure of specific proteins. Alternatively, specific mutations can be introduced into cloned genes and the mutated genes then introduced into intact organisms (e.g., yeast and mice); again, comparison of the normal and mutant organisms provides clues about the in vivo functioning of the encoded protein.

In this chapter we consider some basic concepts in genetics and various genetic techniques that are useful in studying how proteins carry out specific cellular processes and in what order specific proteins function. In the first section, we review basic properties of mutations; in the second, we discuss the isolation of mutants and the characterization of mutations using classical genetic analyses. We then describe the various steps in the

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mapping of mutations, that is, the procedures for locating mutations on particular chromosomes, in regions within chromosomes, and in relation to one another. In the fourth section, we discuss the use of recombinant DNA techniques presented in Chapter 7 to isolate and clone mutation-defined genes from relevant DNA libraries. This approach has permitted the identification and cloning of numerous human disease-linked genes since the mid-1980s. Finally, in the last section of the chapter, we consider molecular techniques for introducing cloned genes, including deliberately mutated genes, into the genome of eukaryotes.

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As the discussion in this and the previous chapter illustrates, the marriage of two genetic disciplines, classical genetics and recombinant DNA technology, forms a powerful approach for understanding biological function. Chapter 7 focused on the protein-to-gene strategy, that is, using knowledge about the sequence of a normal protein to prepare probes for isolating its corresponding gene from a library of cloned DNA. Most of this chapter focuses on the gene-to-protein strategy, that is, using mutation-defined genes to identify normal proteins:

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